

Case Reports

Erythrocytosis Caused by an Erythropoietin-Producing Breast Adenocarcinoma

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A NUMBER OF NEOPLASMS have been associated with the secretion of erythropoietin and the production of erythrocytosis. The following case report documents the first such association with breast cancer.

Report of a Case

The patient, a 46-year-old cigarette-smoking woman, noted a right breast mass in 1982 but concealed it from medical attention until February 1984. At this time the center of the breast was missing, the cavity measuring 14 by 7 cm, and nearly all the rest was indurated with neoplasm. Several axillary nodes, as much as 1 cm in diameter, were palpable. Laboratory tests elicited the following values: hematocrit 0.67 (67%), leukocyte count 11.5×10^9 per liter (11,500 per μ l), and platelet count 200×10^9 per liter (200,000 per μ l). The red cell volume (chromium 51 method) was increased (2,100 ml, with 1,435 ml predicted), and the plasma volume with radioiodinated serum albumin was normal (2,200 ml, with 2,154 ml predicted). Arterial blood gases include a P_{O_2} of 8.35 kPa (63 mm of mercury), with a carboxyhemoglobin of 0.045 (4.5%), normal being less than 0.037 (3.7%) (study not repeated). An intravenous pyelogram showed a borderline small left kidney at 12.3 cm. Urine catecholamine levels were elevated at 1,375.4 nmol per day (252 μ g per 24 hours), the normal being less than 627.7 nmol per day (115 μ g per 24 hours). Metanephrine values were at the upper limit of normal at 5.5 μ mol per day (1.0 mg per 24 hours). Bone and liver scans did not show distant metastases or splenomegaly.

She had blood pressure readings as high as 208/120 mm of mercury, and her hypertension was treated with hydrochlorothiazide, 25 mg, plus triamterene, 50 mg, given twice a day plus sodium restriction. A biopsy was done that confirmed infiltrating ductal adenocarcinoma. An estrogen-

receptor assay was positive at 15 fmol of estradiol bound per milligram of cytosol protein, and a progesterone-receptor assay was negative at 3 fmol of progesterone bound per milligram of cytosol protein. Specimens from the biopsy and peripheral blood serum were sent for erythropoietin assay (see "Methods" section). Both showed elevated levels of erythropoietin, and propranolol hydrochloride, 20 mg three times a day, and methyl dopa, 250 mg twice a day, were added for further blood pressure control. Irradiation of 50.4 Gy (5,040 rad) was given to the breast and node-bearing areas. Tamoxifen citrate was also given. The neoplasm shrank, but it was still fixed to the chest wall and centrally ulcerated. She was admitted for a debulking simple mastectomy, with an admission hematocrit of 0.48. The operation was accomplished the end of April 1984. Infiltrating cancer, apparently viable, was present near the deep margins. Pectoral muscle was involved, as were lymphatic vessels. An additional radiation boost of 14 Gy, using electron beams, was given to the whole area. On day 35 after the operation a blood specimen submitted for erythropoietin determination showed that the erythropoietin had fallen to normal levels (see Table 1). Catecholamine levels were still elevated. The tamoxifen therapy was continued.

The patient was admitted to hospital in July 1984 for treatment of a ruptured sigmoid diverticulum with peritonitis. Surgical and antibiotic therapy was successful, and she was discharged without evidence for recurrent neoplasm and without a return of erythrocytosis. She continues to have hypertension but is free of breast cancer recurrence as of July 1987, having a hemoglobin concentration of 134 grams per liter (13.4 grams per dl), a hematocrit of 0.40, no abnormalities on a chemistry panel, and normal chest film and left mammogram at that time, 3 1/2 years after presentation.

Methods

All specimens were assayed by the exhypoxic polycythemic mouse assay (0.4 atm, 16 hours per day; total 219 hours).¹ Serum was injected as a single dose (1 ml per mouse, 5 mice per group) on day 5 after hypoxia, and radioactive iron (0.5 μ Ci per mouse) was given on day 7. The percent incorporation values of ⁵⁹Fe-labeled erythrocytes were determined 72 hours after administering the iron. Values were converted to equivalent units per liter of erythropoietin with references to the standard curve established for the Second International Reference Preparation of erythropoietin.

The tumor tissue (9.2 grams) was homogenized in 32 ml distilled water, freeze-thawed three times, and spun (10,000g for 15 minutes) to remove particulate matters. One milliliter extract was given to each assay mouse (5 mice per group) on days 5 and 6 and processed as described. The antierythropoietin antibody used here was prepared in rabbits against partially purified human urinary erythropoietin (3,200 IU per mg potency).² The patient's serum and tissue extracts were incubated with the antibody for one hour at 37°C and again at 4°C overnight. Goat anti-rabbit γ -globulin was added and the mixture incubated for one hour at 37°C and spun at 10,000g for 20 minutes to remove precipitates.² The supernatants were assayed as above.

(Bohnen RF, Banisadre M, Gulbrandson RN, et al: Erythrocytosis caused by an erythropoietin-producing breast adenocarcinoma. *West J Med* 1990 Apr; 152:417-418)

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Supported in part by the Veterans Administration, and grant AM 24027 from the National Institutes of Health, Bethesda, Md.

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TABLE 1.—Erythropoietin Assay Results

Materials Assayed	% RBC- ⁵⁹ Fe Uptake*	Equivalent U/liter
Saline	0.31 ± 0.04	ND
Erythropoietin		
50 U	2.12 ± 0.40	50
200 U	6.89 ± 0.76	200
800 U	13.93 ± 1.65	800
Normal human serum, female	0.55 ± 0.12	ND
Patient's serum, before	9.43 ± 1.10	420
Patient's serum, before, plus antierythropoietin	0.61 ± 0.31	ND
Patient's serum, after	0.87 ± 0.21	ND
Tissue extract	5.77 ± 0.87	150
Tissue extract plus antierythropoietin	0.33 ± 0.05	ND

ND=not detectable, RBC-⁵⁹Fe=erythrocytes labeled with radioactive iron

*The results from 5 mice per group are given as the mean plus 1 standard error of the mean.

Discussion

When the patient presented with a high hematocrit and a locally advanced breast cancer, ectopic erythropoietin hormone production was a theoretically possible cause. Leukocyte and platelet counts were normal, the erythrocyte volume was increased, an intravenous pyelogram revealed no renal mass, and a liver-spleen scan was normal. A breast biopsy was needed for estrogen- and progesterone-receptor determinations, and arrangements were made to study erythropoietin values on specimens of blood and biopsy tissue. Both were elevated. She also had hypertension, and catecholamine values were elevated; these findings persisted after irradiation and mastectomy, even though the hematocrit had fallen to 0.40. There is no likely connection between the presence of the two humoral abnormalities.

Neoplasms associated with the ectopic production of erythropoietin include renal cell carcinoma, cerebellar hemangioblastoma, hepatic angiosarcoma, hepatoma, pheochromocytoma, large renal cysts, uterine fibromyoma, and tumors of the thymus, lung, adrenals and ovaries.³⁻¹⁰ As in the present study, the increased production of erythropoietin in most of these cases was documented using the polycythemic mouse assay, which provides a quantitative evaluation of biologically active erythropoietin from human and animal sources.⁵⁻⁹ Although the polycythemic mouse assay is relatively insensitive and cannot reliably detect erythropoietin levels below 50 U per liter, erythropoietin levels in patients with tumor-associated erythrocytosis have been generally high—420 U per liter in this patient—and easily detectable. The radioimmunoassay for erythropoietin,¹¹ now available from commercial sources, is a more sensitive assay procedure and can be used to assess physiologically significant changes in erythropoietin production in clinical disorders of erythropoiesis. We have not been able to find any previous reports in the literature of a primary breast cancer associated with erythrocytosis. Although some fall in the hemoglobin and hematocrit levels due to radiotherapy of the chest wall would be expected, this should in fact result in an increase of the level of erythropoietin and not a diminution as occurred in this patient. Therefore, a fall in both the hematocrit and erythropoietin to normal levels after eradication of the tumor by irradiation and surgical therapy strongly suggests that the breast cancer in this patient was the source of the excessive erythropoietin production. This is further rein-

forced by the presence of large amounts of erythropoietin in the neoplastic tissue as found by our assays.

Adenocarcinoma of the breast should be added to the list of neoplasms to be considered in the differential diagnosis of unexplained or "inappropriate" erythrocytosis.

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Prenatal Diagnosis of Noonan's Syndrome in a Female Infant With Spontaneous Resolution of Cystic Hygroma and Hydrops

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THE NOONAN SYNDROME is one of multiple congenital anomalies that may occur on a sporadic basis or in a pattern consistent with an autosomal dominant inheritance.^{1,2} The pathogenesis remains unknown and the expression is variable.^{1,2} It has been associated with a spectrum of congenital abnormalities. Some of the phenotypic malformations include ptosis, pterygium colli, cryptorchidism, short stature, heart defect, and the jugular obstructive lymphatic sequence.^{1,2}

Cystic hygromas are congenital malformations of the

(Izquierdo L, Kushnir O, Sanchez D, et al: Prenatal diagnosis of Noonan's syndrome in a female infant with spontaneous resolution of cystic hygroma and hydrops. *West J Med* 1990 Apr; 152:418-421)

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